# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| Applicant: | Cevc *et al.* | Art Unit: | 1646 |
| Serial No.: | 09/890,371 | Examiner: | Bruce D. Hissong |
| Filing Date: | April 8, 2002 | Atty. Docket No. | VOS-020/ 2200437.120US1 |
| Title: | Transnasal Transport/Immunisation with Highly Adaptable Carriers | Confirmation No. | 1865 |

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

June 28, 2007
Date of signature and of mail deposit

Robbin Graffius
Robbin Graffius

## DECLARATION OF DR. GREGOR CEVC

Dear Sir:

Responsive to the Final Office Action mailed on January 29, 2007, I Gregor Cevc declare as follows.

1. I obtained a BSc. In Physics in 1975, finished advanced studies in Biochemistry in 1977, obtained a MSA degree in Physics in 1979, and a Ph. D. degree in Medical Biophysics in 1981, all from the University of Ljubljana (Slovenia). My *curriculum vitae* summarizing my educational background, professional experience and number of publications is attached as Exhibit A

2. I am currently employed as the CEO at IDEA AG, which is the assignee of the above-referenced U.S. Patent Application Serial No. 09/890,371 ("the Application"), after

having served in different teaching positions at University of Ljubljana (SLO), Essen University (DE), and the Technical University of Munich (DE).

3. I am an inventor of U.S. Patent Application Serial No. 09/890,371. I am familiar with the Application and its pending claims, and have reviewed the Final Office Action of January 29, 2007.

4. I understand that in the Final Office Action the Examiner rejected claims 54-103 for obviousness over Cevc *et al.*, *Biochem. Biophys. Acta* **1368**: 201-215 (1998) ("Cevc") in view of Drejer *et al.*, *Diabetic Med.* **9**: 335-340 (1992) ("Drejer") and further in view of U.S. Patent No. 4,383,993 to Hussain *et al.* ("Hussain").

5. For the reasons described in the following paragraphs, the claimed invention would not have been obvious to me or to a scientist with ordinary skill in the fields of pharmacology, biology, medicine, biochemistry, biophysics, or the like.

6. The Application claims methods of *transnasally* administering a pharmaceutical composition including an active ingredient and a carrier. The carrier contains a penetrant that includes a minute fluid droplet surrounded by a coating including a lipid and a surfactant (or a more soluble form of the lipid), which provide certain characteristics for solubilization, aggregation and/or elastic deformation energy.

7. The Cevc reference, of which I am an author, describes experiments with a *transdermal* composition used to administer insulin. The composition includes soybean phosphatidylcholine and a surfactant such as sodium cholate. The reference explains that the driving force causing the composition to penetrate the skin is created by a difference in water concentration across the skin. This defines a *hydration force* resulting in delivery of agents across the skin barrier. The first "chief finding" identified at page 204 in the Cevc reference is that "[t]ransepidermal water activity gradient can push the hydrophilic entities into and across the skin if their resistance to penetration is small enough." Thus, the reference indicates that *transdermal* delivery results from the presence of a *transepidermal water activity gradient.* The conclusion was later confirmed by several independent researchers. The lipid carriers described in the reference are designed so as to enable lipid aggregate penetration through the *transdermal barrier* driven by this *hydration force.* As stated at page 208, "[t]he match of the high membrane

deformability and of the good carrier sensitivity to the transepidermal osmotic stress also maximizes the speed of carrier penetration through the skin."

8. Importantly, the Cevc reference does *not* discuss or imply *transnasal* compositions or administration. This is because the *transepidermal water activity gradient* necessary for *transdermal* delivery in the reference *does not exist* in the *strongly hydrated* nasal mucosal membranes. The hydration force driving transdermal delivery is simply *absent* from the *transnasal* barrier traversed by the compositions as claimed. Therefore, it is my opinion that a any scientist reading the Cevc reference would not reasonably consider applying the disclosed composition nasally.

9. It was *completely unexpected* when my co-inventors and I discovered that compositions as identified in the claims could provide highly adaptable penetrants for *transnasal* delivery across the nasal mucosa, despite a high water content on *both* sides of this mucosal barrier (in part due to a high humidity concentration associated with exhaled air). In the Application, itself, we expressed our surprise that the ultradeformable lipid vesicles could be administered nasally:

> The present invention is, in view of the prior art, *particularly surprising* since ultradeformable lipid vesicles *would seem unsuitable for the purpose of transnasal delivery* taken that they were reported to date to cross barriers, such as skin, only under non-occlusive conditions, that is *in the presence of a strong trans-barrier water concentration gradient* (Cevc *et al.* 1995; Paul and Cevc, 1995), *which is believed <u>not</u> to exist in the strongly hydrated nasal mucosa.*" Application, page 16 (emphasis added).

10. Furthermore, the Cevc reference does not discuss designing a composition to provide the characteristics identified in the claims, including a penetrant in the form of a minute fluid droplet with a coating of at least two substances that differ by at least a factor of 10 in solubility, the substances forming aggregates with specified diameter limitations, the more soluble substance solubilizing the droplet, and/or the coated droplet having a particular elastic deformation energy as claimed. These features allow for efficient transfer across a *transnasal*

barrier. In contrast, at page 211 the Cevc reference discloses carriers described generally as "self-optimizing mixtures of lipids," and does not teach the specific claimed features of the penetrant components, which contribute to the carrier's ability to be delivered *transnasally.*

11. I understand that the Examiner suggested combining the Cevc reference with the Drejer and Hussain references. I reviewed these references, and I understand that Drejer teaches nasal administration of insulin with didecanoyl-L-alpha-phosphatidylcholine as an absorption enhancer. Whilst this phospholipid, advocated for nasal use by Drejer, carries similar headgroup as some of the phospholipids (phosphatidylcholines) recited in the Application, the "Drejer phosphatidylcholine" cannot form large bilayer vesicle aggregates, as is requested in the Application, but rather self-assembles into small aggregates in micellar form, owing to is too high water solubility; this is also one of the reasons why didecanoyl-L-alpha-phosphatidylcholine can act as a nasal absorption enhancer. The "Drejer phosphatidylcholine" therefore falls outside the scope of phospholipids claimed in the Application. If one tried to use "Drejer phosphatidylcholine" instead of a surfactant, i.e. in combination with any of the lipids claimed in the Application, a (lipid dependent) proportion of "Drejer phosphatidylcholine" would bind to the large bilayer vesicle aggregates. This would diminish the amount of "Drejer phosphatidylcholine" available for absorption enhancement and thus reduce beneficial effect of Drejer invention (see also item 17 for related discussion), clearly demonstrating that the latter and the Application teach in different directions.

12. I understand that Hussain discloses a composition for nasal administration of progesterone and 17-β-estradiol, which can be formulated with Tween-80 as a solubilizing agent. There is nothing in Hussain's disclosure, however, which would teach combined use of Tween with another (lipid) component to form aggregates with specified diameter limitations and elastic properties. To the contrary, anyone trying to use such a combination aiming to promote progesterone and 17-β-estradiol solubility, in my conviction, would discover that the sex hormone molecules are no longer solubilised, but rather incorporated into larger aggregates. It is also worth noting that Hussain requires use of nasal ointments or nasal gels, whereas the Application does not necessarily request that.

13. The claims of the Application would not have been obvious to me or to another a scientist skilled in the art of drug delivery reading the combination of Cevc, Drejer and Hussain, at least for the reasons given above. This combination of references does not teach or suggest a method of transnasally administering an active ingredient using a carrier containing a penetrant that includes a minute fluid droplet surrounded by a coating of at least two substances, which provide the characteristics identified in the claims for solubilization, aggregation and/or elastic deformation energy.

14. As discussed above, the Cevc reference is directed to carriers for transdermal rather than transnasal administration. Although Hussain and Drejer disclose transnasal compositions, neither reference provides detail regarding the shape or form of the administered composition, which is important for effective transnasal administration according to the Application, as both of them essentially only teach enhanced (Dreyer) diffusion of solubilised (Hussain) drugs across nasal mucosa. Importantly, none of the cited references provides a teaching or suggestion about designing a composition to provide the characteristics identified in the claims, that is, to include a penetrant in the form of a minute fluid droplet with a coating of at least *two substances* that differ by at least a factor of 10 in solubility, the substances forming aggregates with specified diameter limitations, the more soluble substance solubilizing the droplet, and/or the coated droplet having a particular elastic deformation energy as claimed. These attributes of the claimed penetrant promote the attainment of ultradeformable aspects, which provide for the efficient transfer of the composition across the transnasal barrier.

15. Furthermore, I and another scientist skilled in the art of drug delivery would not have had any reason to combine the Cevc reference, which relates to a transdermal formulation, with the Hussain and Drejer references relating to specific transnasal compositions; if anything, one would wish to avoid addition of another lipidic component, as is stated in items 11 and 12. Nor would there be any reason to combine Drejer and Hussain, which disclose different transnasal compositions, as both "Drejer phosphatidylcholine" and Hussains Tween 80 are non-ionic surfactants. Neither Drejer nor Hussain suggests that combining *both* Tween-80 and phosphatidylcholine in a composition would result in any useful transnasal method. I am convinced that two derived combination of the two substances would not provide a useful

carrier, as the resulting aggregate would be too small, and nearly certainly in the form of a micelle rather than of bilayer vesicle.

16. In fact, Drejer actually teaches away from transnasal administration of a composition containing a lipid and a detergent, such as the Tween 80 of Hussain. Drejer at page 339 states that "[c]ertain detergents at high concentrations disrupt and even dissolve biological membranes" and, in contrast, "the formulation used in the present study caused only slight irritation, probably because the substances used are naturally abundant in humans." Thus, Drejer teaches away from any combination with Hussain.

17. Furthermore, the Drejer reference identifies some difficulty even with the dosage form it discloses. Although bioavailability of 8.3% compared to intravenous injection was obtained for the transnasal formulation, *nasal irritation* was found to *increase* at the higher dose that tended to provide higher bioavailability, and to *increase* with a repeated number of sprayings (see pages 338-339 and Tables 4-5).

18. In conclusion, the claimed invention simply would not have been obvious in view of the cited references. I or another drug delivery expert would have no reason to combine these references, and even in view of the combination would not reasonably expect to succeed in reaching the claimed invention. This is particularly true because the Cevc reference suggests that the compositions it discloses would *not* be suitable for *transnasal* administration, and the Drejer reference identifies disadvantages of a formulation including a detergent (like Hussain's), and of higher doses and repeated transnasal administration of the disclosed compositions.

19. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: Gregor Cevc

Dr. Gregor Cevc

Dated: 30-5-07

Exhibit A

**Prof. Dr. Gregor Cevc**
**CEO**

**Curriculum Vitae**

PERSONAL DETAILS

| | |
|---|---|
| Date and Place of Birth: | 20.10.1951 in Ljubljana, Slovenia |

PROFESSIONAL AND ACADEMIC TRACK RECORD

| | |
|---|---|
| | IDEA AG, Munich |
| 04/1998 - | CEO |
| | The Technical University of Munich, School of Medicine |
| 02/1998 – 03/2001 | Professor and Lab. Head |
| | University of Essen (GHS), University Clinics |
| 05/1987 - 02/1988 | Assistant Professor of Medical Biophysics |
| | Laboratory for experimental Urology |
| 04/1982 - 02/1988 | Laboratory Chief |
| | University of Ljubljana, Medical Faculty, Institute for Biophysics |
| 11/1975 - 04/1982 | TA and Lecturer of Biophysics |
| | Max-Planck Institute for biophysical Chemistry, Göttingen, Department of Spectroscopy |
| 1979 - 1980, 1981 | Visiting Scientist |
| | Institut J. Stefan, Department for Theoretical Physics |
| 11/1975 - 04/1979 | Research Officer (part time) |
| | Department of Solid State Physics |
| 11/1974 - 11/1975 | Researcher |
| 06/1973 - 11/1974 | Part time Research Assistant |

EDUCATION AND QUALIFICATIONS

Postgraduate

| | |
|---|---|
| 23.03.1981 | Philosophiae Doctor |
| 26.06.1979 | Magister Scientiae |
| 1975 -1977 | Biochemistry, Biophysics |
| 1974 - 1976 | Solid state physics |
| 1974-1981 | University of Ljubljana, Slovenia |

Pregraduate

| | |
|---|---|
| 23.10.1974 | Graduate (BSc.) |
| 1970 - 1974 | Technical Physics |
| 16.09.1972 | Graduate |
| 1971 - 1975 | History of Art |

Exhibit A

Universities

| | |
|---|---|
| 1970 - 1977 | University of Ljubljana |
| 1978 - 1979, 1981 | |
| 1979 - 1980 | Georg-August-Universität, Göttingen |

AWARDS

| | |
|---|---|
| 1985 | C. E. Alken Prize |
| 1984 | Award of Boris Kidric Foundation |
| 1974 | Preseren Award for Students (Physics) |

BOOKS AND SCIENTIFIC PAPERS

| | |
|---|---|
| 1995 | Phospholipids:Characterization, Metabolism and Novel Biological Applications, AOCS Press, Champain, Il. (coeditor and coauthor) |
| 1993 | Phospholipids Handbook, Marcel Dekker, New York (editor and coauthor) |
| 1987 | Phospholipid Bilayers, Wiley-Interscience, New York (with D. Marsh) |
| 1973- | (Co)Author of over 150 scientific papers |

PATENTS & INVENTIONS

| | |
|---|---|
| 10 | International patent families with close to 200 national applications and over 60 issued patents |
| 5 | Invention disclosures for IDEA |

EDITORIAL & REVIEWING ACTIVITIES

| | |
|---|---|
| 1998 - | Current Topics in Biochemical Research - Editorial Board Member |
| 1996 - | Chemistry and Physics of Lipids - Editorial Board Member |
| 1993 - 1998 | J. Chem. Society / Faraday Transactions - Editorial Board Member |
| 1992 - 2001 | Journal of Liposome Research - Editorial Board Member |
| 1990 - | Reviews on Biomembranes (BBA) - Editorial Board Member |
| 1989 - | Biochimica et Biophysica Acta (BBA) - Editorial Board Member |
| • | Referee for >30 international scientific journals |
| • | Peer-reviewer of 9 national and international research councils |

RELEVANT PAST CONSULTANCIES

- Natterman Phospholipids
- Lancaster Group
- Hoechst-Marion-Roussel

PERSONAL PROFESSIONAL MEMBERSHIPS

- German Biophysical Society
- European Pharmaceutical Biotechnology Association